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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/613,591	07/10/2000	William J. Boyle	A-378CIP5	9711

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AMGEN INCORPORATED
MAIL STOP 27-4-A
ONE AMGEN CENTER DRIVE
THOUSAND OAKS, CA 91320-1799

EXAMINER	
DEBERRY, REGINA M	
ART UNIT	**PAPER NUMBER**
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/613,591	Applicant(s) BOYLE ET AL.	
	Examiner Regina M. DeBerry	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,17-25 and 39-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,17-25 and 39-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3,17,21* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Status of Application, Amendments and/or Claims

Applicant has stated that the references listed on the IDS filed 08 November 2000 (Paper No. 3) and 31 December 2001 (Paper No. 21) were not supplied because they were submitted to the Office in prior applications. The references have not been located. Regretfully, the references listed cannot be considered at this time. Applicants are invited to cite a particular reference(s) that they want to be considered.

The information disclosure statement filed 26 September 2001 (Paper No. 17) was received and complies with the provisions of 37 CFR §§1.97 and 1.98. It has been placed in the application file and the information referred to therein has been considered as to the merits.

The Formal Drawings filed 08 August 2001 (Paper No. 13) have been received.

The amendment filed 22 March 2002 (Paper No. 24) has been entered in full. Claims 2-16, 26-38 and 43-61 were cancelled. Applicant's election with traverse of Group IV (claims 1, 17-25, 32 and 39-42) in Paper No. 24 is acknowledged. The traversal is on the grounds that all species should be considered in the case because the searches would substantially overlap. Applicant states that the species would involve the same search terms and many references concern more than one species. Claim 1 is drawn to approximately 16 species. A search of prior art may disclose references, which concern more than one species, however because many of the instant species are diverse from one another, a search of all of the species in one application would result in undue burden. Furthermore, a search of references is also

directed to anticipation of the invention, and therefore requires a search of relevant literature in many different areas of subject matter. The requirement is still deemed proper and is therefore made FINAL. Applicant timely traversed the restriction (election) requirement in Paper No. 24.

Specification

The disclosure is objected to because of the following informalities: In Example 13, the specification refers to incorrect figures (page 167, line 7 and line 20).

In addition, there is no reference to IL-Ira which is depicted in Figures 30A and 30B.

Sequence Rules

The instant application fails to fully comply with the sequence rules 37 CFR 1.821-1.825 because each disclosure of a sequence embraced by the definitions set forth in the rules fails to refer to the required sequence identifier (SEQ ID NO:). This occurs in Figures 1A, 1B, 2B, 2C, 9A, 9B, 9C, 9D, 9E, 9F, 10, 12A, 12B and 29A-G. Sequences appearing in drawings may be referenced in the drawings themselves or in the corresponding Brief Description thereof. In addition, there is a discrepancy with the sequence of SEQ ID NO:129 and SEQ ID NO:135. The amino acid length of SEQ ID NO:129 is listed as 280 and SEQ ID NO:135 is listed as 202 in Figure 2E, but in the sequence listing, the amino acid length of SEQ ID NO:129 is listed as 281 and the amino acid length of SEQ ID NO:135 is listed as 205.

The specification and drawings should be checked to make sure the sequence identifiers are not missing and that the DNA and amino acid lengths in the figures and sequence listing are the same. Applicants is given the same response time regarding this failure to comply as that set forth to respond to this office action. **A complete response to this office action includes compliance with this sequence rule compliance. Applicant must submit a response to this Office Action and compliance with sequence rules simultaneously.**

Claim Objections

Claim 1 is objected to because of the following informalities: Claim 1 encompasses non-elected inventions and requires amendment to limit to elected invention. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1,17-25 and 39-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating bone loss, which comprises administering a therapeutically effective amount of a purified and isolated OPG protein, IL-I inhibitor and TNF-α inhibitor wherein isolated OPG has at

least amino acid residues 22-185 and wherein OPG is rat (SEQ ID NO:121), mouse (SEQ ID NO:123), or human (SEQ ID NO:125) does not reasonably provide enablement treating "conditions" leading to bone loss and does not reasonably provide enablement for all species and variants of OPG. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification teaches the SEQ ID Nos for rat, mouse and human OPG protein. The specification states that amino acid residues 22-185 define a region of OPG activity (page 154, lines 14-17). The specification discloses a combination treatment of OPG-Fc (22-194) and sTNFR-I or OPG-Fc (22-194) and IL-Ira on adjuvant arthritis in rats in Figures 31A, 31B and Example 14. The specification, however, fails to disclose combination treatments with any species or variant of OPG. Furthermore, the specification does not disclose methods for treating a particular condition leading to bone loss. The specification discloses methods for specifically treating bone loss not the condition. The scope of the instant claims exceeds the scope of the enabling disclosure.

Due to the large quantity of experimentation necessary to treat conditions leading to bone loss and to test a combination of species and variants of OPG with IL-I inhibitors and TNF-α inhibitors in adjuvant arthritis in rats, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, and the breadth of the claims which fail to recite limitations of different species OPG and variants in treating bone

loss, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1,17,19,21 and 25 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1,17, 24 and 25 are indefinite because the meaning of "OPG protein" is unclear. The claims do not convey to the skilled artisan the minimal structural and functional requirements of such polypeptides to satisfy the limitations of the claim.

Claims 19 and 21 are indefinite because of the interchangeable use of "sTNFR-I" and "sTNF-RI".

In addition, claim 21 recites the limitation "the method of claim 17, wherein the sTNF-RI fragment is a 2.6 kD fragment". Claim 17 is drawn to "TNF-α inhibitor". There is insufficient antecedent basis for this limitation in the claim.

Claim 24 is indefinite. The term "etanercept" in claim 24 is a relative term which renders the claim indefinite. The term is listed on page 74, line 10 of the specification. However, the term "etanercept" is not defined by the claim and the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1,17 and 25, 39, 41 and 42 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1,7-14 of U.S. Patent No. Patent No. 6,288,032 B.

In U.S. Patent '032, the claims are drawn to an isolated polypeptide having the biological activity of inhibiting bone resorption. The polypeptides encompass SEQ ID NO:2, SEQ ID NO:4 and SEQ ID NO:6. These SEQ ID Nos represent the amino acid sequences of rat, mouse and human osteoprotegerin (OPG) (see Figure 9 for definition). The polypeptide can be attached to polyethylene glycol. The polypeptide can also be fused to an Fc region of human IgG or a derivative thereof. The patented claims are also drawn to a method of treating a bone disorder comprising administering to a patient an isolated polypeptide of OPG variants having the biological activity of inhibiting bone resorption. The bone disorder is due to excessive bone loss by

conditions such as rheumatoid arthritis, osteopenia and osteomyelitis. The patented method further comprises administering TNF-α inhibitors and IL-I inhibitors.

Claims 18-19 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 7-14 of U.S. Patent No. 6,288,032 in view of Thompson *et al.* WO 93/21947 (IDS #B2, Paper No. 17). Thompson teaches the synergistic effects of combining IL-I and TNF (page 2, lines 24-32). Thompson teaches that TNF inhibitors can be *soluble fragments of TNF receptor proteins*. Thompson teaches that *TNF inhibitors that are useful in the present invention include particularly soluble fragments of TNF receptor proteins, including 30kDa TNF inhibitor and 40kDa TNF inhibitor* (page 3, line 28-page 4, line 5). The instant specification states that *soluble TNF receptor type I is also known as TNFR-I or 30 kDa TNF inhibitor and soluble TNF receptor type II is also known as sTNFR-II or 40 kDa TNF inhibitor* (specification page 29, lines 14-20). Thus Thompson discloses these TNF inhibitors.

Thompson teaches *IL-Ira inhibitor* (page 4, lines 21-28). Thompson uses an *animal model of rheumatoid arthritis to investigate the use of combination therapy with 30 kDa TNF inhibitor and IL-Ira*. Thompson states that the proteins can be modified by the addition of polyethylene glycol (PEG) or any other repeat polymer to increase their circulating half-life and/or to decrease immunogenicity (page 3, line 27-page 4, line 4). Thompson demonstrates that IL-Ira and TNF alone inhibited joint swelling but the combination of the two caused an additive inhibitory effect of swelling (pages 14-17).

It would have been obvious to one of ordinary skill in the art to use the teachings of Thompson to design the instant methods of claims 18-19 for treating bone loss by administering IL-Ira and sTNFR. Patent '032 discloses that OPG, IL-I inhibitors and TNFα inhibitors can be administered to treat bone loss and bone loss due to disorders such as rheumatoid arthritis. Thompson teaches the use of specific IL-I and TNF inhibitors in rheumatoid arthritis animal models.

Claims 20-22 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 7-14 of U.S. Patent No. 6,288,032 B in view of Fisher *et al.* WO 98/01555. Fisher teaches a 2.6 kd fragment of sTNFR-I (page 7, lines 6-12, page 30, line 28-page 31, line 6 and page 45, lines 25-29). Fisher teaches the use of PEG (page 32, lines 17-19) and molecular weights of PEG polymers between 20kDa to 35kDa (page 33, lines 4-14). Fisher teaches the conjugation of 30kDa PEG to sTNFR-I 2.6 (page 40, lines 7-14 and page 41, lines 28-35).

It would have been obvious to one of ordinary skill in the art to use the teaching of Fisher to design the instant methods of claims 20-22 for treating bone loss by administering 30 Kd PEG-sTNFR-I, 2.6 kd sTNFR-I fragment and sTNFR-I fragment comprising 30Kd PEG. Patent '032 discloses that OPG, IL-I inhibitors and TNFα inhibitors can be administered to treat bone loss and bone loss due to disorders such as rheumatoid arthritis. Fisher teaches that these fragments listed above are TNF inhibitors and these derivatives still maintain the inhibitory activity (page 4, lines 7-25).

Claim 23 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 7-14 of U.S. Patent No. 6,288,032 B in view of Murray *et al.* (abstract, Ann Pharmacother. (11):1335-8 Nov 31 1997) Murray teaches fusions of TNFR and the Fc region.

It would have been obvious to one of ordinary skill in the art to use the teachings of Murray to design the instant method of claim 23 for treating bone loss by administering a fusion of TNFR and Fc. Patent '032 discloses that OPG, IL-I inhibitors and TNFα inhibitors can be administered to treat bone loss and bone loss due to disorders such as rheumatoid arthritis. Murray teaches that TNFR:Fc proteins have been effective in animal models of rheumatoid arthritis.

Claim 40 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 7-14 of U.S. Patent No. 6,288,032 B in view of Miyagi *et al.* (abstract, Shinshu Igaku Zasshi 40/6 567-75, 1992) and Nieves *et al.* (Neurology 44 (9) 1687-92 Sept.1994). Miyagi teaches that levels of cytokines IL-I alpha and TNF are increased in multiple sclerosis patients compared with controls. Nieves teaches that multiple sclerosis (MS) patients have bone loss. MS patients are at increased risk for bone disorders such as osteoporosis and pathologic fracture.

It would have been obvious to one of ordinary skill in the art to use the teachings of Miyagi and Nieves to design the instant method of claim 40 for treating bone loss and

bone loss due to conditions such as multiple sclerosis. Patent '032 discloses that OPG, IL-I inhibitors and TNFα inhibitors can be administered to treat bone loss and bone loss due to various disorders. Miyagi teaches increased levels of the cytokines in MS patients and Nieves teaches bone loss in MS patients.

Conclusion

No claims are allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (703) 305-6915. The examiner can normally be reached on Mondays-Fridays 8:00 a.m. - 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-7939 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

RMD
May 31, 2002

ELIZABETH KEMMERER
PRIMARY EXAMINER